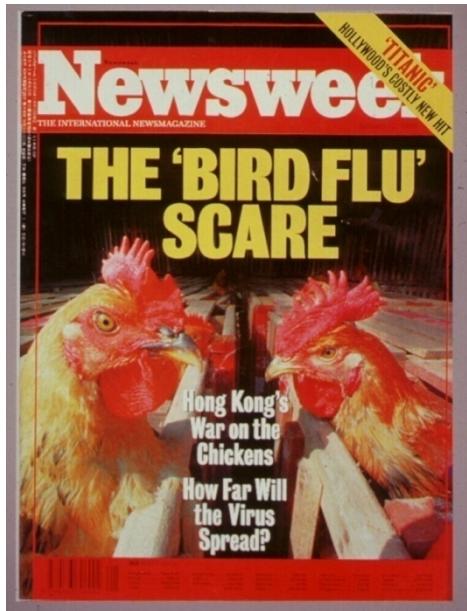


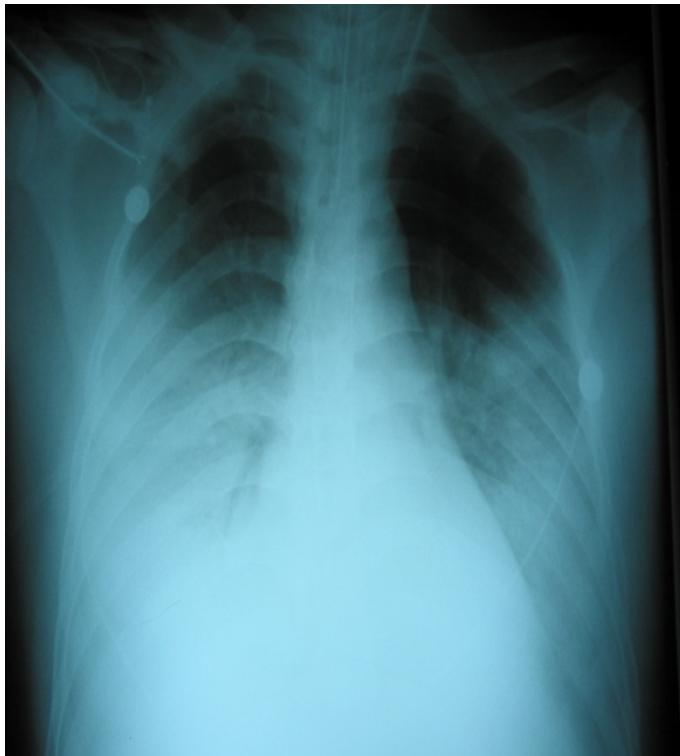
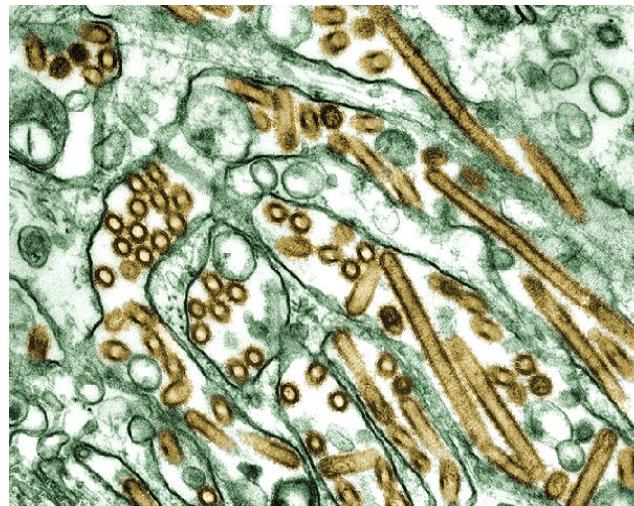


# H5N1 Influenza Virus: Overview

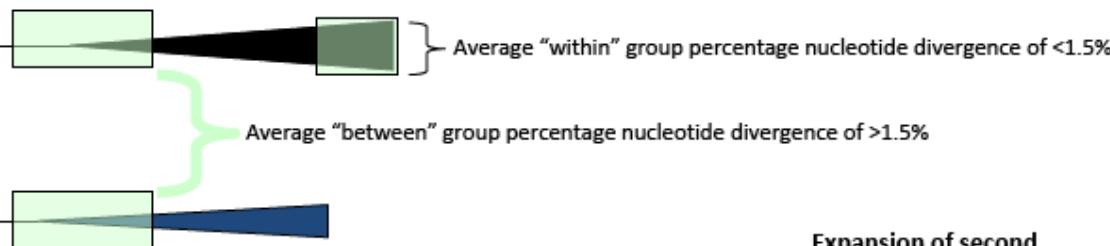
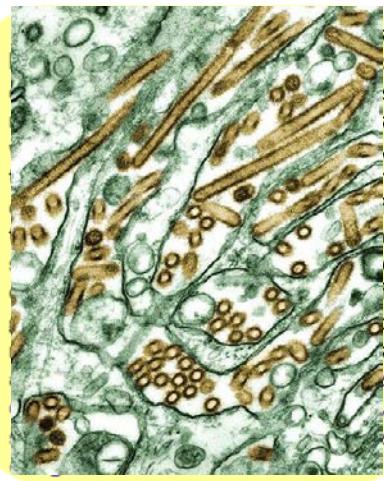
Malik Peiris  
Centre of Influenza Research  
School of Public Health  
The University of Hong Kong



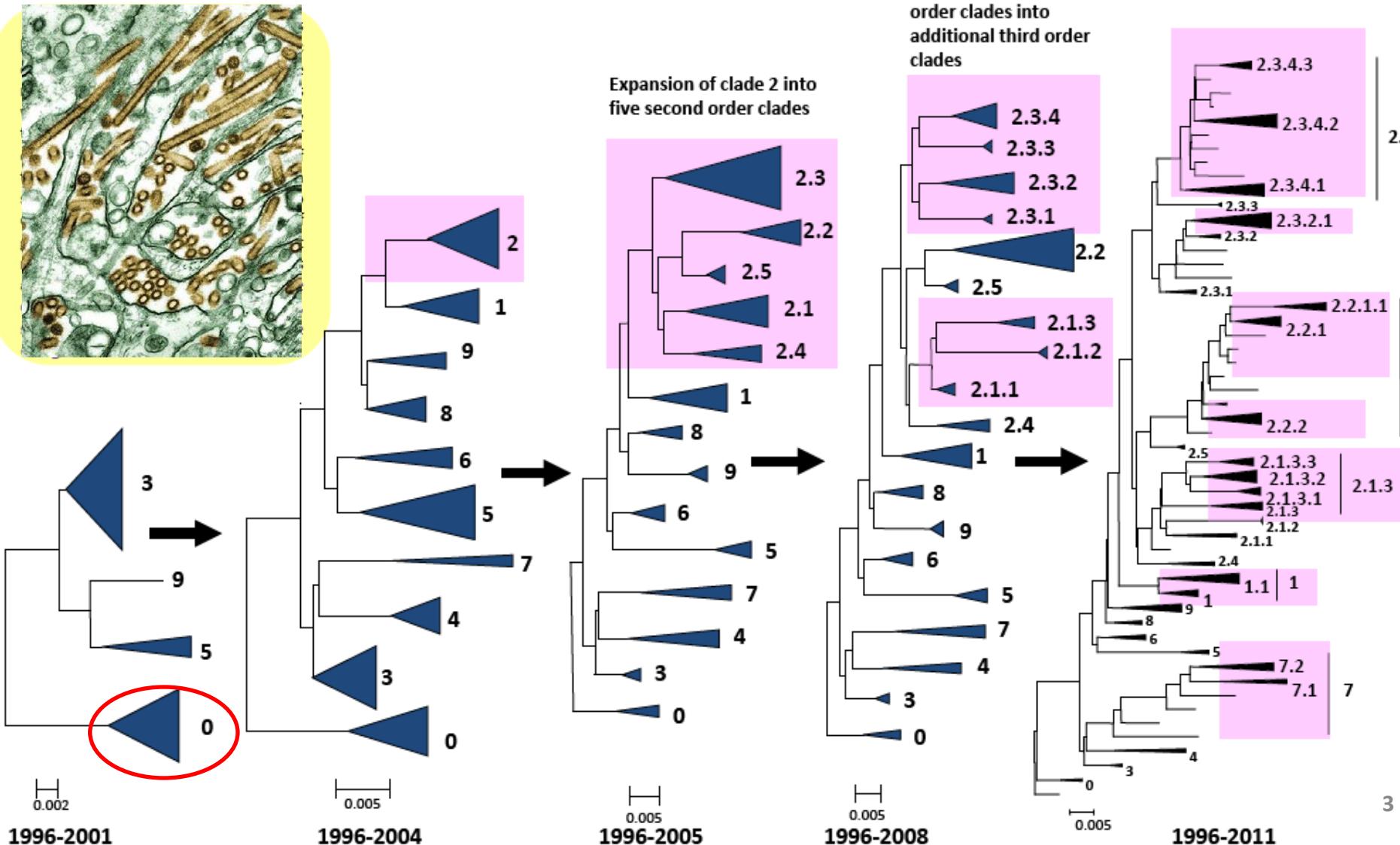
# *H5N1: The virus and the disease*



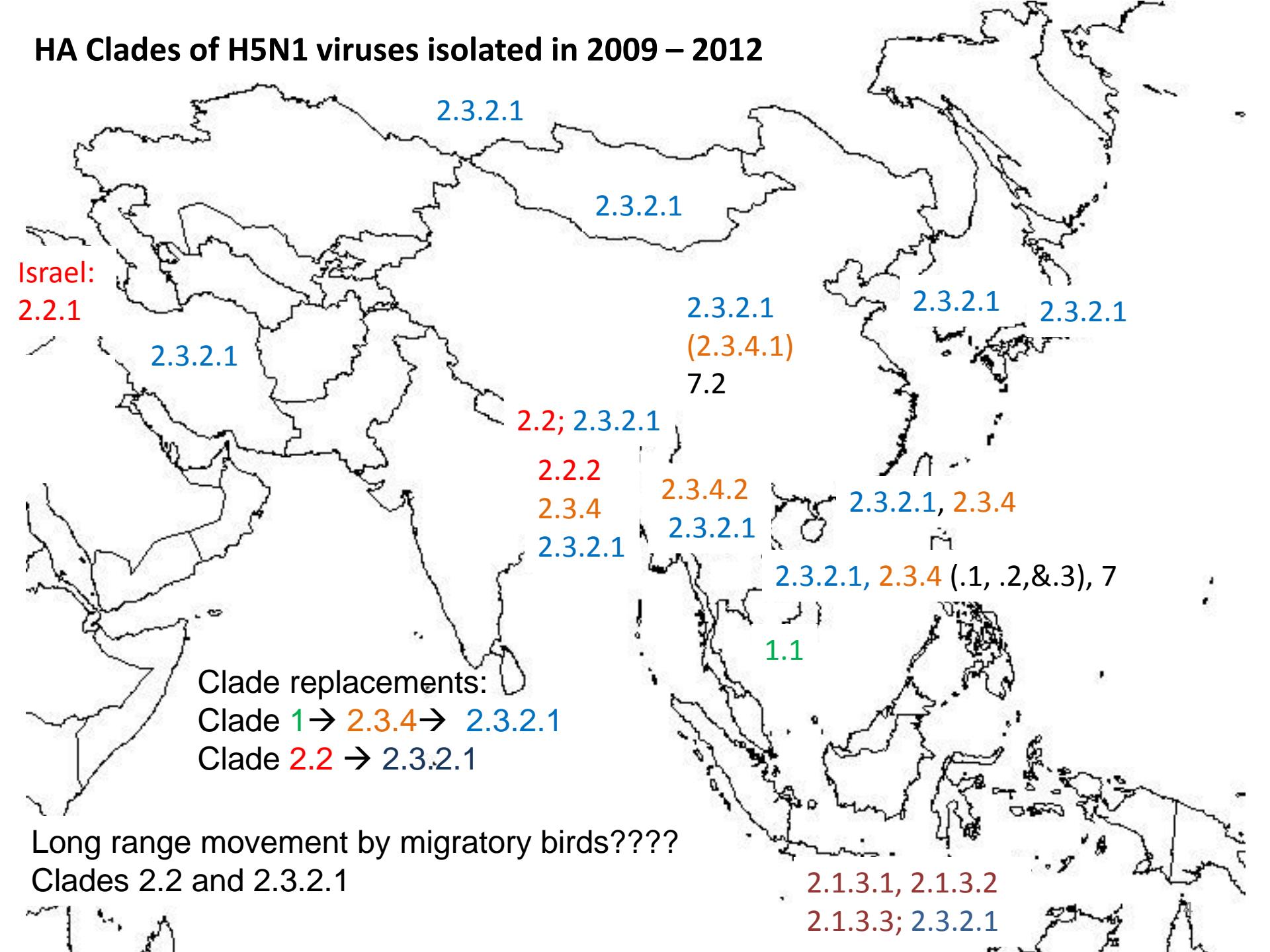
# Evolution of the Asian H5 Hemagglutinin



Expansion of first, second and third order clades into additional second, third and fourth order clades



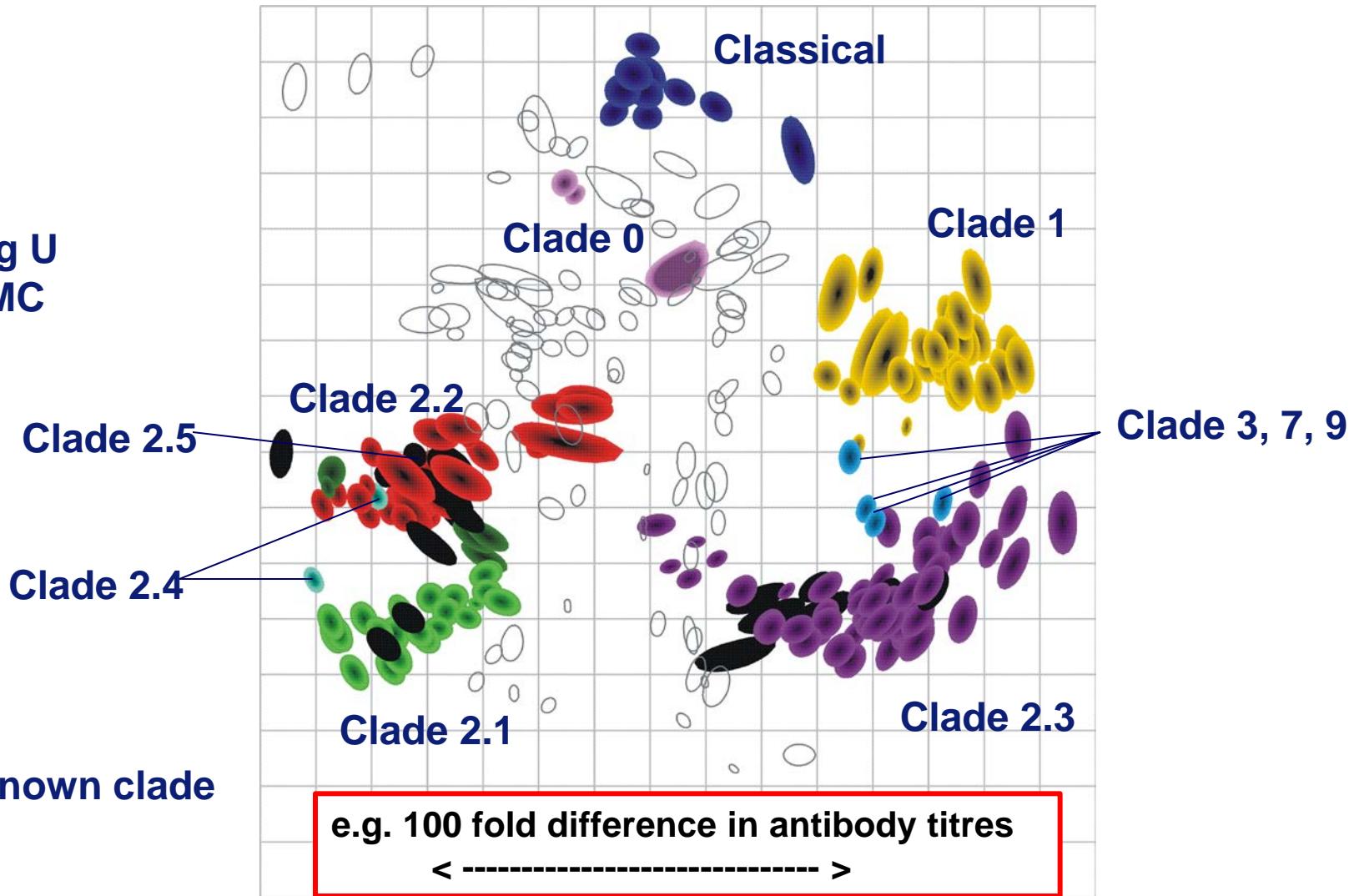
## HA Clades of H5N1 viruses isolated in 2009 – 2012



# H5 influenza antigenic map

Data from:

- CDC
- St Jude
- Hong Kong U
- Erasmus MC



Black: unknown clade

e.g. 100 fold difference in antibody titres

< ----- >

# Antigenic and genetic characteristics of zoonotic influenza viruses and development of candidate vaccine viruses for pandemic preparedness

September 2012



World Health Organization

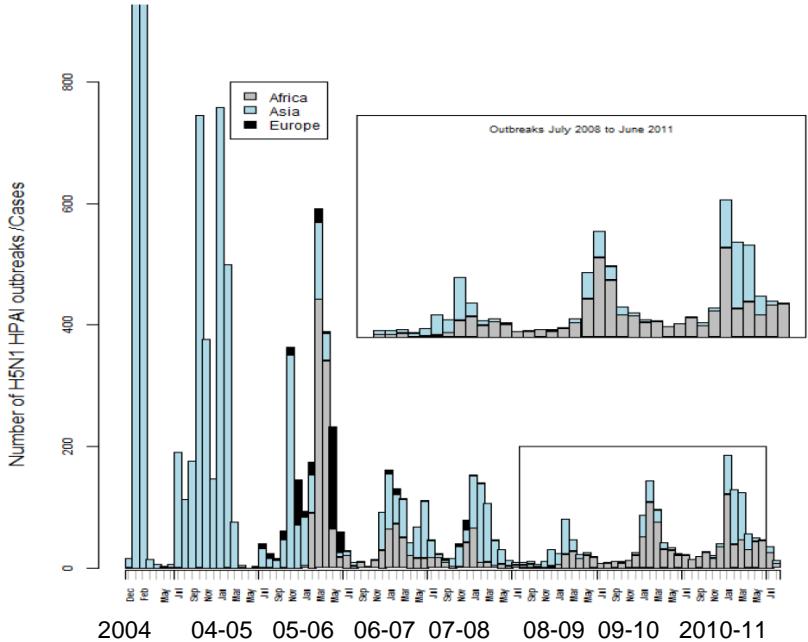
Table 3. Status of influenza A(H5N1) candidate vaccine virus development (September 2012)

Candidate vaccine viruses	Clade	Institution*	Available
A/Viet Nam/1203/2004 (CDC-RG; SJRG-161052)	1	CDC and SJCRH	Yes
A/Viet Nam/1194/2004 (NIBRG-14)	1	NIBSC	Yes
A/Cambodia/R0405050/2007 (NIBRG-88)	1.1	NIBSC	Yes
A/duck/Hunan/795/2002 (SJRG-166614)	2.1	SJCRH	Yes
A/Indonesia/5/2005 (CDC-RG2)	2.1.3.2	CDC	Yes
A/bar-headed goose/Qinghai/1A/2005 (SJRG-163222)	2.2	SJCRH	Yes
A/chicken/India/NIV33487/2006 (IBCDC-RG7)	2.2	CDC/NIV	Yes
A/whooper swan/Mongolia/244/2005 (SJRG-163243)	2.2	SJCRH	Yes
A/Egypt/2321-NAMRU3/2007 (IDCDC-RG11)	2.2.1	CDC	Yes
A/turkey/Turkey/1/2005 (NIBRG-23)	2.2.1	NIBSC	Yes
A/Egypt/N03072/2010 (IDCDC-RG29)	2.2.1	CDC	Yes
A/Egypt/3300-NAMRU3/2008 (IDCDC-RG13)	2.2.1.1	CDC	Yes
A/common magpie/Hong Kong/5052/2007 (SJRG-166615)	2.3.2.1	SJCRH	Yes
A/Hubei/1/2010 (IDCDC-RG30)	2.3.2.1	CDC	Yes
A/barn swallow/Hong Kong/D10-1161/2010 (SJ-003)	2.3.2.1	SJCRH	Yes
A/chicken/Hong Kong/AP156/2008 (SJ-002)	2.3.4	SJCRH	Yes
A/Anhui/1/2005 (IBCDC-RG6)	2.3.4	CDC	Yes
A/duck/Laos/3295/2006 (CBER-RG1)	2.3.4	FDA	Yes
A/Japanese white eye/Hong Kong/1038/2006 (SJRG-164281)	2.3.4	SJCRH	Yes
A/goose/Guiyang/337/2006 (SJRG-165396)	4	SJCRH	Yes
A/chicken/Viet Nam/NCVD-016/2008 (IDCDC-RG12)	7.1	CDC	Yes
A/chicken/Viet Nam/NCDV-03/2008 (IDCDC-RG25A)	7.1	CDC	Yes

Candidate vaccine viruses in preparation	Clade	Institution	Availability
A/chicken/Bangladesh/11RS1984-30/2011-like	2.3.4.2	CDC	Pending
A/Indonesia/NIHRD11771/2011-like	2.1.3.2	NIID	Pending

# H5N1: A virus entrenched Unlikely to be eradicated

## Poultry outbreaks reported to OIE



Data from EMPRESS

## Outbreaks in wild birds & poultry

Highly Pathogenic Avian Influenza H5 confirmed outbreaks

26 October 2011 - 26 April 2012



Highly Pathogenic Avian Influenza H5 confirmed outbreaks

29 May - 29 November 2012



# Why H5N1 virus is difficult to eradicate from poultry flocks



**Backyard flocks**

## “Trojan” Ducks

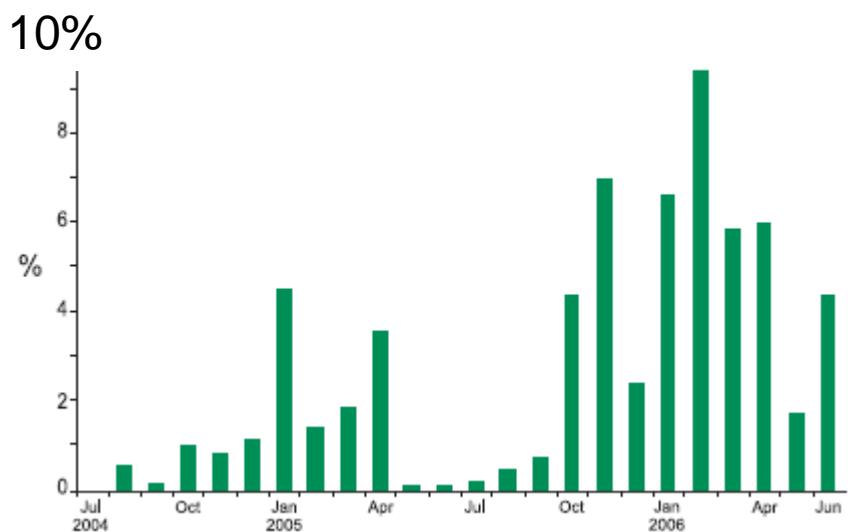
- Strum-Ramierz *et al* 2004
- Hulse-Post *et al* 2005
- Songserm *et al* 2006
- Gilbert *et al* 2006

## Live poultry markets

- Kung *et al* 2003
- Kung *et al* 2007
- Lau *et al* 2007
- Santhia *et al* 2009
- Indriani *et al* 2010
- Samaan *et al* 2011

# The H5N1 paradox

Exposure ~~=~~ Human Infection / Disease



## Environmental Sampling for Avian Influenza Virus A (H5N1) in Live-Bird Markets, Indonesia

Risa Indriani,<sup>1</sup> Gina Samaan,<sup>1</sup> Anita Gultom, Leo Loth, Sri Indryani, Rma Adjid, Ni Luh Putu Indi Dharmayanti, John Weaver, Elizabeth Mumford, Kamalini Lokuge, Paul M. Kelly, and Darminto

EID 2010

83 live poultry markets in West Java sampled for environmental H5N1 contamination : 2007/2008

47% had evidence of H5N1 contamination

*Exposure is ubiquitous; (infection) / disease is very very rare.  
Exposure is necessary, but not sufficient.*

# Virus transmission dynamics and critical intervention points



Poultry farms



Wholesale poultry  
market



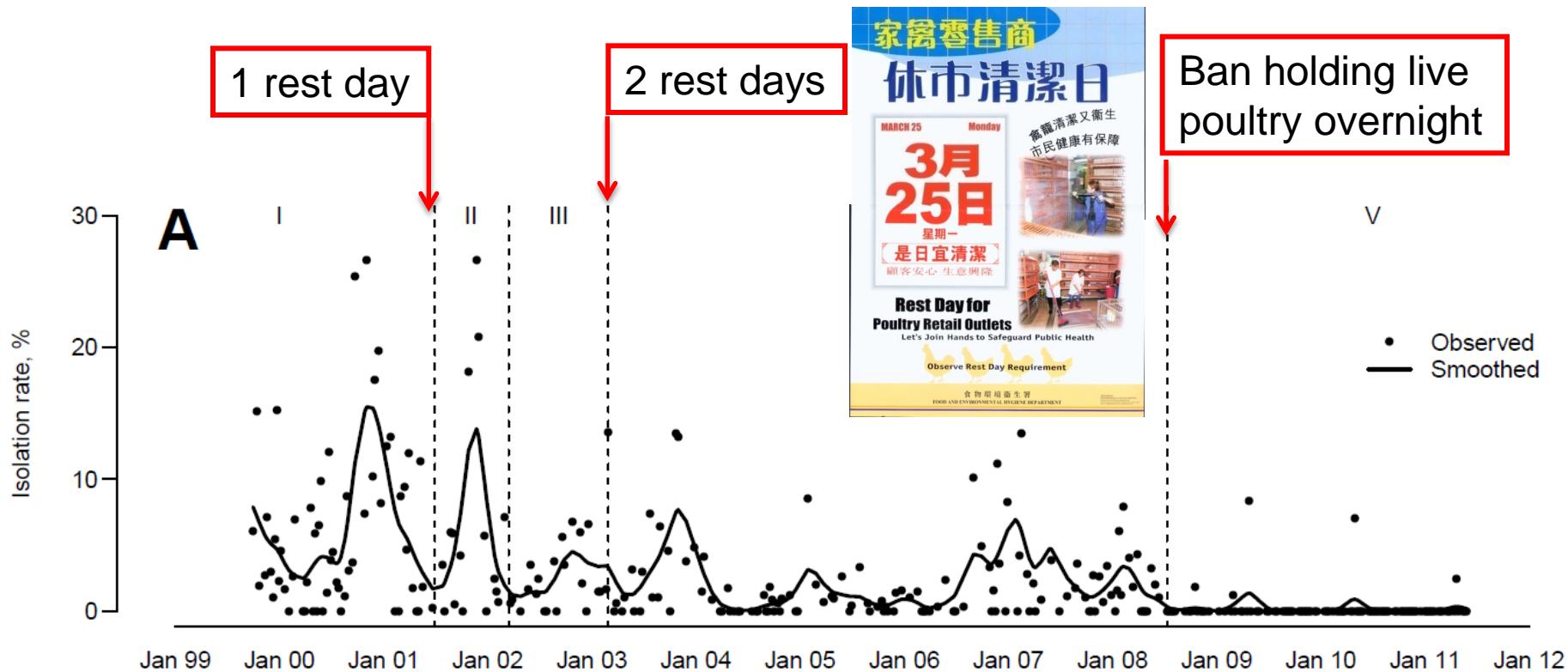
Retail poultry  
Market

*Kung et al Avian Dis 2003; Lau et al EID 2007; Leung et al 2012;  
Kung et al Emerg Infect Dis 2007; Samaan et al 2012; Indriani et al 2010<sup>10</sup>*

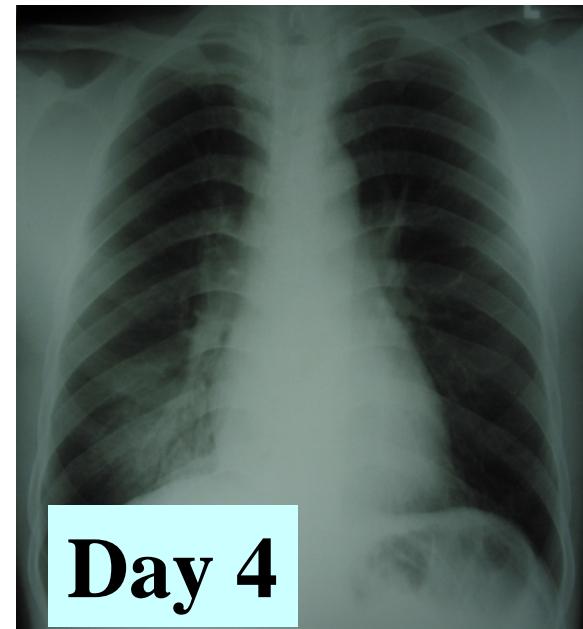
# Evidence based interventions in live poultry markets

## *Isolation rates of H9N2 viruses in chicken*

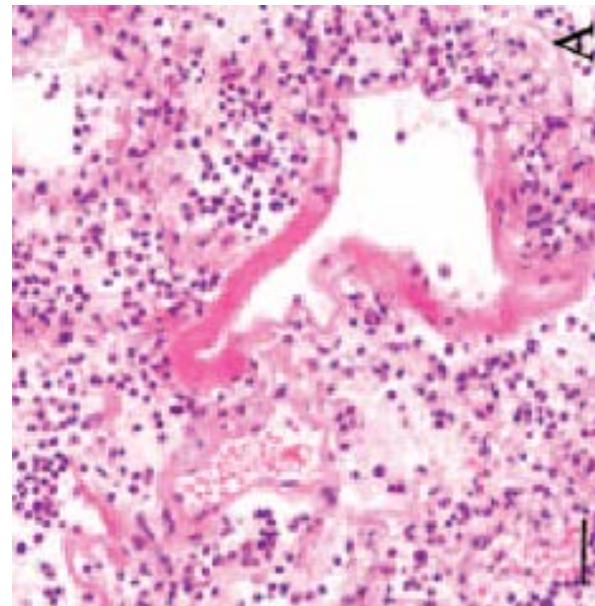
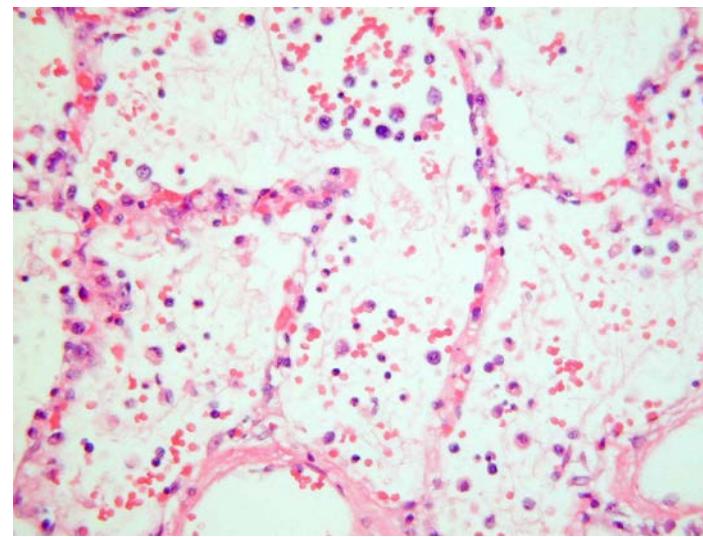
1999-2011; monthly surveillance; 5-8 FEHD poultry markets; 53,541 samples



# Human H5N1 disease



Day 4



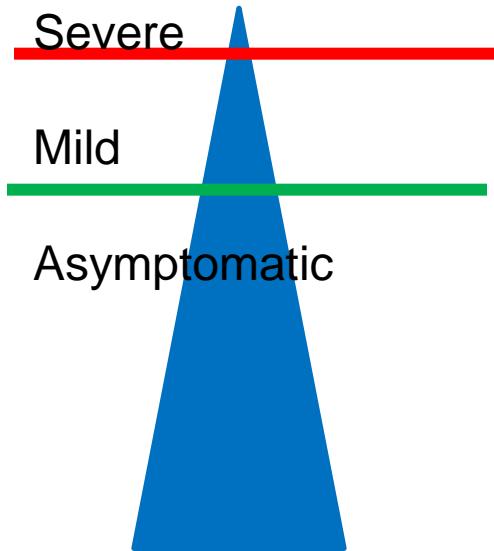
# H5N1: Clinical presentation

- **Incubation period:** typically 2-5 days; onset to death: median 9-10 days
- **Severe viral pneumonia:**
  - Rapidly progressing primary viral pneumonia, previously healthy younger persons.
  - Associated with lymphopenia, thrombocytopenia, moderate liver / renal dysfunction .
  - Progress to ARDS, MODS, hemophagocytosis
  - Extra-respiratory dissemination can occur (CNS, GI, viremia) and may contribute to pathology, but major cause of death remains respiratory pathology.
- **Mild “flu-like” syndrome**
- **Atypical presentations:**
  - Viral encephalitis.
  - Diarrhoeal disease

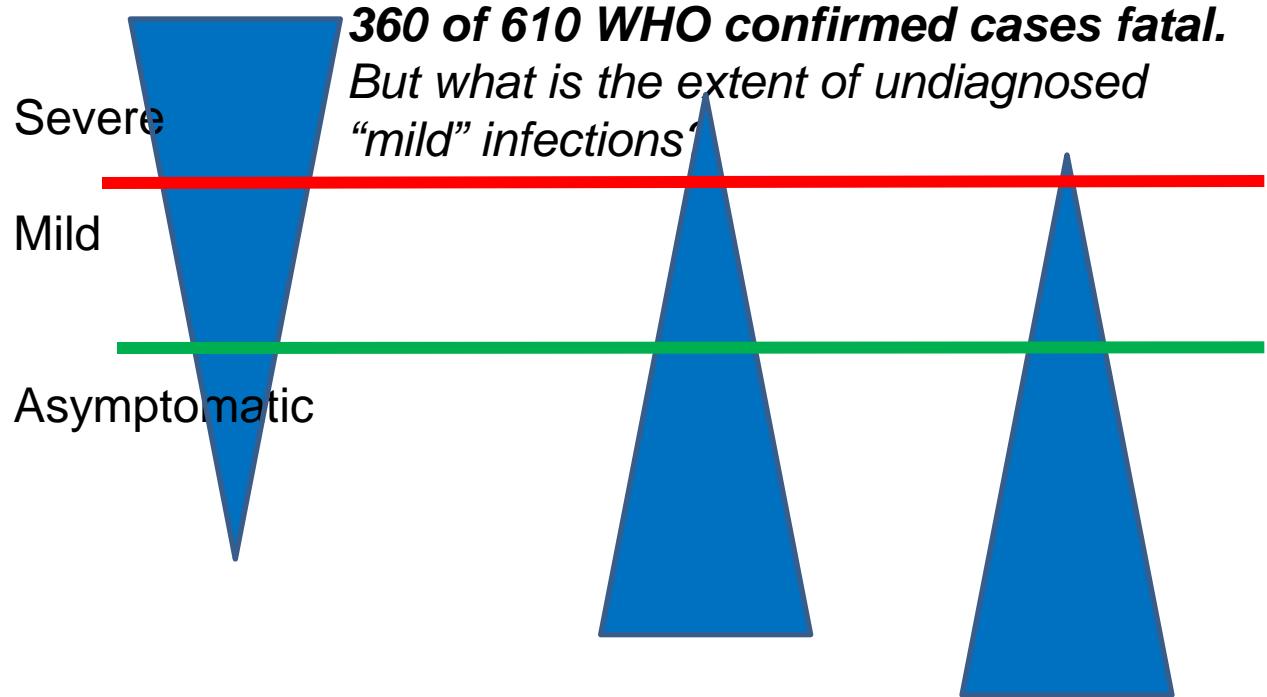
*Yuen et al Lancet 1998; Hien et al NEJM 2004; 350: 1179; Chotpitayasanondh et al EID 2005; Kandun IN et al. NEJM 2006; 355: 2186-94; De Jong et al NEJM 2005; Apisarnthanarak et al EID 2004; Yuen et al Lancet 1998; De Jong et al NEJM 2005; Oner et al NEJM 2006; WHO NEJM 2008; Shu et al JID 2010; Gu et al Am J Pathol 2008; Zhang et al Hum pathol 2009*

# Severity of human H5N1 disease?

## Pandemic H1N1



## Where does the H5N1 “iceberg” sit



Wu et al CID 2010

Riley et al PLoS Med 2011

Steens et al Am J Epid 2011

Miller et al Lancet 2010

Van Kerkhove et al. PloS One 2011; 6: e14582

Wang et al. Science 2012; 335: 1463

Van Kerkhove et al. Science 2012

**Problems: Serological cross-reactivity with seasonal influenza.**

e.g. Leroux-Roels et al., Lancet 370, 580 (2007).

Lack of prior immunity

High viral replication competence

## High / prolonged viral replication

*De Jong et al Nat Med 2006  
Salomon et al JEM 2005*

## Tissue tropism

*Shinya et al Nature 2006; van Reil et al 2006  
Nicholls et al – Nat Med 2007  
Yao et al FASEB J 2008*

## Viral dissemination

*De Jong et al Nat Med 2006  
Buchy et al J Clin Virol 2007  
Gu et al Lancet 2007*

Immune evasion

## H5N1 lung pathology / disease

## Dysregulation of host responses

### In patients:

#### Cytokines (serum)

*Peiris et al Lancet 2004;*

*De Jong et al Nat Med 2006  
(correlated with virus load)*

*Lee et al CID 2008 (Human flu) Tumpey et al JV 2000 (H5N1 HP vs LP)*

#### Apoptosis (lung)

*Uiprasertkul et al EID 2007*

### In ferrets / mouse lung

*Cameron et al JV 2008 (IFN response genes; CXCL10)*

*Perrone et al PLoS Path 2008 (HP/LP H5N1; H1N1  
Maines et al Immunol Rev 2008 (HP/LP H5N1)*

# *Summary*

- ***Currently circulating H5N1 viruses:***

- Virus unlikely to be eradicated from poultry
- Continues to diversify genetically → may become pandemic (pandemic H1N1 gene in swine)
- Rarely infects humans, but severe outcome when they do
- Infected human index case: human-to-human transmission very rare, and even then, is not sustained.
- Host susceptibility ?? genetic factors, ?? Other
- Severity in ferrets → variable

- ***Mammalian transmissible H5N1 viruses:***

- Field viruses continue to diversity genetically → changes in transmissibility to humans may occur in field?
- Antivirals and vaccines are available to protect those working with these viruses (c.f. SARS)
- What biosafety measures are appropriate?